RESEARCH ETHICS

Benefits, risks and ethical considerations in translation of stem cell research to clinical applications in Parkinson's disease

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Stem cells are likely to be used as an alternate source of biological material for neural transplantation to treat Parkinson's disease in the not too distant future. Among the several ethical criteria that must be fulfilled before proceeding with clinical research, a favourable benefit to risk ratio must be obtained. The potential benefits to the participant and to society are evaluated relative to the risks in an attempt to offer the participants a reasonable choice. Through examination of preclinical studies transplanting stem cells in animals and the transplantation of fetal tissue in patients with Parkinson's disease, a current set of potential benefits and risks for neural transplantation of stem cells in clinical research of Parkinson's disease are derived. The potential benefits to research participants undergoing stem cell transplantation are relief of parkinsonian symptoms and decreasing doses of parkinsonian drugs. Transplantation of stem cells as a treatment for Parkinson's disease may benefit society by providing knowledge that can be used to help determine better treatments in the future. The risks to research participants undergoing stem cell transplantation include tumour formation, inappropriate stem cell migration, immune rejection of transplanted stem cells, haemorrhage during neurosurgery and postoperative infection. Although some of these risks are general to neurosurgical transplantation and may not be reduced for participants, the potential risk of tumour formation and inappropriate stem cell migration must be minimised before obtaining a favourable potential benefit to risk calculus and to provide participants with a reasonable choice before they enrol in clinical studies.

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Stem cells are considered to be an alternate source of biological material for cell restorative treatments, particularly for the treatment of neurodegenerative disorders with no effective long-term treatment such as Parkinson's disease. Parkinson's disease affects roughly 1% of the population >65 years old in North America and is one of the most likely neurological disorders where the transplantation of stem cells may be assessed because there are nearly two decades of clinical experience associated with neural transplantation of human fetal tissue. Currently, more than 350 patients worldwide have received fetal ventral mesencephalic (FVM) tissue transplants in various open-label and in two double-blind, randomised, placebo-controlled clinical trials with variable results.[1 2] In one placebo-controlled clinical trial, some improvements in all 10 subjects <60 years of age was observed.[1] The other clinical trial failed to meet its clinical end point, with no overall marked improvement in the motor features of 34 patients with Parkinson's disease.[2] Despite the results with these two clinical trials transplanting FVM tissue, participant groups with less severe Parkinson's disease did show considerable clinical improvement in both trials.[1 2] Ultimately, neural transplantation of FVM tissue will probably not become a routine therapeutic practice owing to limited tissue availability. As such, stem cells may provide an unlimited source of biological material that can be cultured under stringent quality-controlled conditions and made available to the medical community for therapeutic purposes. The transplantation of stem cells for Parkinson's disease may also provide proof-of-concept of the ability of stem cells to be used as an alternate source of biological material. Most importantly, the transplantation of stem cells will be used in restorative strategies to treat other incurable neurological conditions such as stroke or spinal cord injury.

Before proceeding with clinical research on the transplantation of stem cells in participants with Parkinson's disease, several ethical criteria must be considered.[3] Of particular interest in our study is the ethical requirement of having a favourable probability of benefit to risk ratio for human research to proceed (45CFR46.111(a)).[4] The moral analysis of whether risks are reasonable in relation to potential benefits is perhaps the most important determination institutional review boards (IRBs) must consider, as it attempts to offer research participants a reasonable choice. Determination of the current potential benefits and risks of clinical research on neural transplantation of stem cells for the treatment of Parkinson's disease is especially timely because research protocols on cell replacement are likely to be submitted for IRB review in the near future. Examination of potential benefits and risks to patients after stem cell transplantation will be crucial to adequately inform patients before requesting their consent (45CFR46.116(a)(2), (a)(3), (a)(6), (b)(1)).[4] Through the examination of preclinical studies on the transplantation of stem cells in parkinsonian animal models and clinical research transplanting FVM tissue in research participants, we derive a current set of potential risks and benefits of stem cell transplantation for clinical research of Parkinson's disease.

Abbreviations: DBS, deep brain stimulation; FVM, fetal ventral mesencephalic; IRB, institutional review board

In an attempt to inform IRBs and other research ethics boards or committees, we will deal with areas where potential risks in the transplantation of stem cells may be minimised to reach a favourable probability of benefit to risk ratio.

A favourable probability of benefit to risk ratio for research on humans

To obtain a favourable probability of benefit to risk ratio before beginning clinical research, IRBs are instructed to measure risks and potential benefits systematically. Risk refers to the probability that physical, psychological, economic, legal or social harm occur and could affect both people and society at large.[5] By contrast, a benefit denotes something of value that can occur directly to participants or to society.[5] The main benefit to society is the development of generalisable knowledge, whereas research participants may benefit by relief from disease or disability and from receiving clinically relevant information.[5 6] Although generalisable knowledge is a benefit to society, most research risks are assumed by the participant; therefore, IRBs must ensure that human participants are exposed only to an ethically justifiable amount of risk.[6] More specifically, the US Federal regulation under the ''Common Rule'' states that the risks to participants should be reasonable in relation to anticipated benefits for clinical research and the importance of knowledge to society (45CFR46.111(a)(2)).[4] Furthermore, the risks to research participants are minimised using established protocols or procedures consistent with sound design (45CFR46.111(a)(1)).[4]

An ethical framework for the analysis of risks and the probability of benefits for IRBs requires that procedures in clinical research be separated on whether they are designed solely to deal with the research question or if they have potential therapeutic benefit.[6 7] For components that are designed solely to answer the research question, the risks must first be minimised and then weighed against the potential benefit of knowledge to be gained. For components that offer therapeutic benefits to research participants, the risks are assessed in relation to the potential direct benefits to participants and whether there is clinical equipoise.[6 7] Clinical equipoise refers to the state where genuine uncertainty over which intervention, be it an experimental arm or control (including placebos), exists in the expert community as a whole.[8] If both therapeutic and non-therapeutic components pass their separate tests, then the risks posed to participants in the study are reasonable when compared with the expected benefits to the patient and society.

Potential benefits to research participants undergoing stem cell transplantation and to society

FVM tissue transplantation has shown beneficial effects on some patients by long-term reduction in clinical symptoms such as tremors, bradykinesia (slowness of movement), akinesia (absence of normal movement) and postural impairment.[1 9] Specifically, some motor improvements in all 10 subjects, <60 years of age, were observed in one clinical trial.[1] In two clinical cases, FVM tissue transplantation has also led to a 70% beneficial reduction or full cessation of parkinsonian drugs.[10] Although several studies show some improvement in motor behaviour in participants after surgery, long-term assessment shows that such treatments are not fully effective in all patients with Parkinson's disease, with 34 subjects showing no overall improvement after transplantation.[2] Side effects such as the development of postoperative dyskinesias (abnormal involuntary movements and postures) have also been reported in 56.5% of patients who were taken off drugs and are a major concern.[2]

Clinical studies of FVM tissue transplantation and preclinical stem cell animal experiments using both rodents[11] and non-human primates[12] suggest that stem cell transplants may provide benefits to research participants and to society and thus, may be used as an alternative to fetal tissue in cell restoration strategies for Parkinson's disease. However, the first clinical studies that transplant stem cells in patients with Parkinson's disease will most likely include older patients who display severe parkinsonian symptoms. Relief of motor symptoms will probably not occur in older participants in the initial phases of clinical research. Although the biological mechanisms controlling non-dopaminergic features of Parkinson's disease are poorly understood, the transplantation of stem cells may not alleviate non-dopaminergic features of Parkinson's disease such as cognitive-declined dementia and psychiatric symptoms.[13] The potential benefits of stem cell grafting to participants with Parkinson's disease should not be overstated and nuanced such that the informed consent procedure explains that the likelihood of success depends on the age of the patient and the severity of symptoms of Parkinson's disease. Future clinical research on the transplantation of stem cells may have to restrict eligibility criteria to include only participants <60 years of age or those who have mild symptoms of Parkinson's disease to achieve considerable clinical improvement.

Perhaps the largest benefit from research on stem cell transplantation would be the production of generalisable knowledge for society. This analysis will be valuable for the treatment of Parkinson's disease, and also provide proof-of-concept whether stem cells could potentially be used to treat other neurodegenerative diseases. Before moving into the clinic, IRBs will need to ensure that risks are minimised so that a favourable probability of benefit to risk ratio is obtained.

Risks to society and direct risks to research participants undergoing stem cell transplantation

Although there may be direct risks to research participants in stem cell transplantation research, there are also social risks. One major social risk in using embryonic stem cells as a source for neural transplantation is that new embryonic stem cell lines would have to be created. The derivation of human embryonic stem cells results in the destruction of the embryo, presenting an ethical dilemma for those that ascribe a considerable degree of personhood to embryos. A reliance on human embryos as a source of embryonic stem cells will require the retrieval of ova from women and the potential harms caused by superovulation and oocyte retrieval. A need for human embryos for embryonic stem cell treatments may lead to the commodification of embryos and eggs from women. However, most of the risks of stem cell transplantation will be directed to research participants, and include tumour formation, inappropriate stem cell migration, immune rejection of transplanted stem cells, haemorrhage during neurosurgery and postoperative infection.

Tumour formation with embryonic stem cells

Clinical studies on FVM tissue transplantation indicate that FVM cells when appropriately harvested rarely proliferate and form tumours after transplantation.[14] The risk of tumour formation in preclinical studies on stem cell transplantation depends on the type of stem cell, its proliferative capacity and the site of transplantation. Owing to their high propensity to divide, several animal experiments have shown that embryonic stem cells may form tumours after transplantation. Specifically, transplantation of undifferentiated embryonic stem cells into the striatum of parkinsonian rats resulted in their spontaneous differentiation into dopaminergic neurones with modest behavioural improvements; however, 5 of 25 rats died owing to teratoma formation, resulting in a calculated risk of 20%.[15] Hence, undifferentiated embryonic stem cells are not suitable for transplantation owing to the risk of unregulated cell

growth. In contrast, animal studies on neural stem cell transplantation have not shown tumour formation. Although the transplantation of neural stem cells minimises the risk of tumour formation, these cells have a limited capacity to spontaneously differentiate into dopaminergic neurones in vivo.[16]

To minimise the risk of tumour formation by embryonic stem cells, many groups have attempted to predifferentiate stem cells into dopamine neurones before transplantation.[11] Of the different approaches used to predifferentiate embryonic stem cells, one method may include the creation of genetically modified embryonic stem cell lines where a gene of interest, such as Nurr1 which promotes dopaminergic cell fate, may be overexpressed.[11] The stable insertion of the gene itself, and the methods used to create genetically modified embryonic stem cells, may pose theoretical risks of physical harm to research participants. Insertional mutagenesis from viral integration in a key regulatory gene may cause tumour formation or other cellular anomalies. In this case, it may be crucial to identify the sites of gene insertion in the creation of stable embryonic stem cell lines or to avoid the use of genetic modification altogether. The difficulty with assessment of risks in preclinical studies on stem cell proliferation after neural transplantation is that tumour formation may occur after a long time, whereas many rodent species used to evaluate such risks have short life spans of <2 years, suggesting that non-human primate studies may be required. The creation of stable stem cell lines using viruses may also pose a theoretical risk of transmitting viral particles to make replication competent viruses.[17] To minimise these theoretical risks, a thorough assessment of genetically modified stem cells should be carried out to ensure their safety. However, the theoretical risks of using genetically modified embryonic stem cells are reasonable when compared with the potential therapeutic benefits of relief of clinical symptoms or reduction in parkinsonian drugs to research participants because no other physiological abnormalities were observed in animals after transplantation of Nurr1-transfected embryonic stem cells,[11] The use of non-viral means of gene delivery would reduce the risk of forming live viruses, and predifferentiation of stem cells by non-genetic means will nullify the risk of using genetically modified stem cells.

Inappropriate stem cell migration and neurological complications

Research participants receiving stem cell transplants may be at risk of experiencing neurological complications owing to stem cell migration from the graft site to inappropriate regions of the brain. Unlike the dense clusters of cells that have limited migrational capacity in FVM tissue transplants in the striatum in animal models of Parkinson's disease, undifferentiated neural stem cells have the capacity to undergo extensive migration from the site of transplantation to non-target sites of the brain through white matter tracts.[18] The abundant evidence of stem cell migration, especially to sites of lesion in the brain through white matter tracts, could cause a risk of abnormal brain function. Even if a low percentage of stem cells migrate to other areas of the brain, this does not mean that the clinical symptoms would not be harmful for the recipient. Potential clinical symptoms due to aberrant stem cell migration after transplantation are predicted in pathological conditions in the brain such as grey matter heterotopias and temporal lobe epilepsy.

Grey matter heterotopias are collections of normal neurones or astrocytes in unusual locations such as the subependymal region (subependymal heterotopias) of the lateral ventricles and the white matter (subcortical heterotopias) below the cortex that result from aberrant migration of cells during cortical development.[19] These neurones have limited maturity and anomalous connectivity, which may result in clinical symptoms of seizures.[20] Medically refractory temporal lobe epilepsy is suggested to be caused by neurogenesis and subsequent migration of ectopic granule cells to the hilus, which along with hilar basal dendrite formation, cause abnormal excitatory synaptic inputs that lead to clinical symptoms of seizures.[21] The propensity of stem cells to migrate may result in a theoretical risk that causes seizure-like symptoms or other brain dysfunction. The potential risk of behavioural manifestation seen from inappropriate stem cell migration may be minimised by predifferentiating neural stem cells before transplantation.

Immune rejection of transplanted stem cells

Cyclosporin is a widely prescribed immunosuppressive drug that prevents rejection after transplantation of solid organs or bone marrow, with long-term use shown to cause hepatotoxicity, nephrotoxicity, hypertension and immune suppression.[22] Clinical studies on FVM tissue grafts have also used cyclosporin at various dosages and durations.[2 8] Studies on transplanting FVM tissue in non-immunosuppressed participants show either no clinical improvement or some clinical improvement in patients, suggesting that immunosuppression may not offer any obvious advantage to graft survival from immune rejection. However, a comparison of immunosuppressive regimens in clinical studies on FVM tissue transplants suggests that well-monitored, long-term immunosuppressive treatment leads to a low immunogenic response to FVM tissue and continued clinical improvement in patients. Specifically, clinical deterioration has been shown to coincide with discontinuation of cyclosporin.[2] This being the case, many studies continue to use immunosuppression to prevent the possibility of graft rejection. As immune rejection may result from the transplantation of stem cells, treatment with immunosuppressive agents will probably be given to transplant recipients as a precaution to prevent rejection. Treatment with drugs is a therapeutic procedure and the possible harm caused by immunosuppressive drugs may be considered reasonable in relation to the potential direct clinical benefits of having a viable tissue graft for research participants.

Neurosurgical haemorrhage and postoperative infection

It is estimated that stereotactic neurosurgery used in the transplantation of FVM tissue may be associated with a 3% risk of intracerebral haemorrhage and postoperative infection. A haemorrhage can arise from the transplantation instrument injuring blood vessels, which may lead to stroke or stroke-like syndrome, including sensory loss, weakness or other neurological problems. Infection of the skin, skull or the meninges can arise owing to inadequate sterilisation of surgical instruments or inadequate postoperative care. To prevent postoperative infection, participants are prescribed antibiotics. The risk of haemorrhage and infection from neurosurgery cannot be minimised for stem cell transplantation procedures; as such risks depend on brain anatomy or postoperative care rather than the use of different surgical instruments, the neurosurgeon or the transplantation protocol. In addition, the risks of infection and haemorrhage with transplantation may be considered to be less than with deep brain stimulation (DBS), which is routinely used to treat tremors. DBS poses additional risks of infection of the skin and brain owing to the presence of a foreign object such as a DBS lead. There are also the risks of repeated surgeries to replace the battery, DBS lead or wire breakage, migration after insertion and medical complications such as paralysis, speech difficulties, seizures, and mood changes such as depression. The surgical risks with DBS can run as high as 25% compared with transplantation surgery.[23]

The risks of haemorrhage and infection from stem cell transplantation may be considered to be reasonable in relation to the benefits to the participant.

Transplantation of infected stem cells

A risk associated with FVM tissue transplantation is the transmission of infectious agents from donor FVM tissue.[24] Stem cells could undergo various screening procedures that are used in clinical studies to test for infections such as hepatitis B, human T lymphocyte virus, HIV, cytomegalovirus and herpes simplex virus, ensuring a safe and reliable source of stored tissue. The risk of contamination from tissue culture and cryoprotectant media may also result from the handling of stem cells. Routine tests for common pathogens such as Staphylococcus, Streptococci, *Escherichia coli* and yeast will have to be carried out. IRBs should be made aware of the breadth of tests carried out to reduce the risk of transmitting infectious agents from stem cells.

Use of placebos and FVM tissue in the design of research on clinical stem cell transplantation

IRBs should be aware that clinical research using stem cells can be designed such that research participants may receive a placebo or another treatment, such as FVM tissue, and that both control arms can influence the harm–benefit ratio. In the case of FVM tissue transplantation, the two double-blind, randomised, placebo-controlled clinical trials used a sham surgical operation as a placebo. Sham surgery included the fitting of a stereotactic frame on the subject, the administration of anaesthetic, drilling of partial burr holes in the skull that did not penetrate the dura, positron emission tomography scans and treatment with antibiotic and immunosuppressive drugs.[2] Results from one placebo-controlled trial showed a dramatic placebo effect in subjects who received the sham surgery,[25] suggesting that a similar control would prove useful in stem cell transplantation research. A sham surgical placebo control for Parkinson's disease is considered to be non-therapeutic as it offers no potential benefit to participants.[26] In such cases, the risks of placebo are to be minimised consistent with sound scientific design (45CFR46.111(a)(1)(i))[4] and should be made reasonable in relation to the knowledge gained from the study.[7] Drilling partial burr holes is consistent with sound scientific design by minimising the risks of infection and haemorrhage, but still maintaining the illusion of a surgical operation to subjects. Similarly, the application of anaesthesia, performing diagnostic positron emission tomography scans and treating subjects in the placebo arm with antibiotics and immunosuppressive drugs would also be warranted to ensure that subjects believe they have received a stem cell transplant.

The placebo is considered to be one of the most rigorous controls to provide an accurate measurement of the biological effectiveness of an intervention that is not due to psychological factors that contribute to healing. Although the placebo effects seen were dramatic in subjects who received a sham surgical operation,[25] the extent of the placebo control itself could in theory differ. As different placebos may cause varying effects on subjects, the effect of placebo in the FVM tissue clinical trials may not fully account for the psychological factors that contribute to the healing process.[26] For example, it may be argued that penetration of the dura by cannula insertion and injection of media-lacking cells would be necessary for analysis of the placebo effect. However, to expose patients in clinical research studies to such a risk would be unethical as it offers no potential therapeutic benefit. Similarly, a trial design consisting of various sham surgical control arms would use many subjects for little scientific insight into the placebo effect. Symptoms may worsen owing to disease progression in subjects receiving a placebo, which may be dependent on the length of the trial. Receiving a placebo with no known therapeutic benefit to subjects changes the risk to probability of benefit ratio and as such, the extent of the sham surgical operation, along with the other procedures involved, will have a major role in the harm–benefit calculus.

One way to resolve the problem of using a non-therapeutic placebo is to design a trial with an active control, such as bilateral DBS in the subthalamic nuclei, which is the surgical procedure currently used to treat patients with Parkinson's disease who no longer respond to medical treatment. Designing a trial comparing FVM tissue with stem cells, instead of a placebo or DBS, may be problematic as FVM tissue grafts are not a true positive control because it is not yet considered to be an established, routine treatment for patients with Parkinson's disease. In addition, comparing FVM tissue with stem cells grafts will not answer the question of whether the neural transplantation of stem cells is better than no treatment and may result in a false negative with a statistical β error.[27] A trial that may result in a false negative would expose participants to unnecessary risks and waste their time and valuable clinical resources (reagents, research money and staff time). Furthermore, using any active controlled trial may require a greater number of participants to obtain a marked improvement of stem cell transplants over the active control, thus adversely affecting power calculations. If it is determined that there is no suitable active control for stem cells, then placebo controls may be used. Sham surgical operations as placebos are components designed solely to address the research question and may be considered to be more ''risky'' than pharmacological or psychological controls and the risks may not be minimised with sound scientific design.[28 29] The risks to participants may be minimised with sound scientific design using a no-surgery arm or one in which all subjects receive transplants have presurgery and postsurgery test scores using a core assessment protocol.[30] However, this may be at the cost of not being able to understand the placebo effect of stem cell transplant surgeries. An active, currently used surgical control such as DBS or no surgery, with presurgery and postsurgery test scores, is more likely to pass a harm–benefit evaluation.

ANALYSIS OF POTENTIAL BENEFITS AND RISKS OF STEM CELL TRANSPLANTATION FOR PARKINSON'S DISEASE

Before proceeding to clinical research of stem cell transplantation for patients with Parkinson's disease, a favourable probability of benefit to risk calculus must be obtained. Neurosurgical haemorrhage, postoperative infection, graft rejection and the transplantation of infected cells are general risks associated with neurosurgery and transplantation medicine when included in a well-designed protocol using appropriate instruments, skilled neurosurgeons and the necessary preoperative tests for contaminants. These risks may not be further minimised for research participants. Moreover, several IRBs and ethics boards alike have permitted clinical research on transplanting FVM tissue, indicating that the risks are reasonable when compared with the potential benefits received by some subjects and the knowledge gained by society. In such cases, if only risks of neurosurgery, infection and immune rejection existed for stem cell transplantation, clinical research may ethically move forward with the transplantation of stem cells for patients with Parkinson's disease.

With the current state of scientific knowledge of stem cell transplantation in rodent[11] and primate[12] animal models, it seems that embryonic stem cells may hold the most promise to relieve parkinsonian symptoms. However, the potential use of adult stem cells has not been ruled out and more research on the subject is needed. The initial risk of tumour formation by

embryonic stem cells may be negated due to predifferentiation; however, the transplantation of embryonic stem cells into parkinsonian animal models has required the genetic modification of embryonic stem cell lines to induce differentiation into dopamine neurones.[11] Additional assays must be carried out to ensure that stable gene integration does not alter cell behaviour and result in uncontrolled cell proliferation or some other medical problem while minimising risks caused to the participant.

The theoretical risk of neurological complications due to inappropriate stem cell migration are not reasonable when compared with the potential benefits gained because these neurological complications may outweigh the potential relief of parkinsonian motor symptoms to participants. The participants' families and society may also be burdened with the additional healthcare costs required for the treatment of various neurological complications. Neurological side effects may be difficult to observe when using animal models as behaviours in animals are not always fully translatable to human disease. At a minimum, the migrational ability of stem cells should be observed for in other regions of the brain posttransplantation. After eliminating or minimising the risk of tumour formation and stem cell migration, the potential benefits and risks with clinical stem cell transplantation for patients with Parkinson's disease should be recalculated to ensure its favourability.

The probability of benefit–risk calculus to participants shifts depending on trial design when using placebo controls such as a sham surgical operation, FVM tissue transplantation, a no-surgery arm, or presurgery and postsurgery assessments. A sham surgery for patients with Parkinson's disease would be considered to be non-therapeutic, as it offers no potential benefit to participants.[25] As such, the risks of placebo are to be minimised consistent with sound scientific design (45CFR46.111(a)(1)(i))[4] and should be reasonable in relation to the knowledge gained from the study. Designing a trial using FVM tissue as an active control for stem cells may lead to a false-negative result. At this stage, it is uncertain if an equivalent known therapeutic can be used as a control for stem cell transplantation and therefore, if placebos are used, the IRB must judge whether the knowledge gained about the placebo effect in stem cell transplantation for patients with Parkinson's disease is ''reasonable'' compared with the risks endured by participants.[6] On achieving a favourable probable benefit to risk ratio as well as satisfying other ethical criteria, clinical research transplanting stem cells for patients with Parkinson's disease may become morally acceptable.

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